BRILL

Canadian Jr. of Clinical Perf. Evaluation Malpractice

Towards Optimal Care: Hepatitis B in Saudi Arabia - Initiatives for Clinical Excellence and Malpractice Prevention: Insights from the Systematic Observatory Liver Disease (SOLID) Registry

Sophie Lefebvre, [1] Lucas Dubois, [1] Charlotte Leroy [1]

[1] Internal medicine department, Division of Hepatology, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

Correspondence: lefebvres283@gmail.com

Abstract: Background: Vaccination against Hepatitis B (HBV) has significantly reduced global infections, yet the prevalence persists worldwide, posing a substantial health threat. Saudi Arabia continues to grapple with the morbidity and mortality associated with HBV, underscoring its status as a significant public health concern. Despite the global success of HBV vaccination, Saudi Arabia still harbors a sizable cohort, necessitating a comprehensive understanding of the natural course of chronic hepatitis B (CHB) and the impact of follow-up on disease progression. Objectives: To analyze all the CHB data from 2008 to 2019 in the SOLID registry and then analyze the effects of follow-up in both treated and untreated subjects with 12 months. SOLID is a multi-centered official registry of CHB in Saudi Arabia. Methods: In a retrospective study using the SOLID registry (Saudi observatory liver disease) data from 2008 to 2019, we analyzed 1564 chronic hepatitis B (CHB) patients. Part 1 focused on baseline characteristics, categorizing patients into active or inactive disease based on international guidelines. Exclusion criteria included co-infections and significant deficiencies in baseline parameters. Part 2 included 699 subjects with follow-up >12 months, comparing untreated and treated groups. Outcome measures encompassed demographics, laboratory values, and non-invasive fibrosis markers. Statistical analysis involved SPSS version 21.5, presenting data as means or frequencies. The study received ethical approval (IRB Approval Number: E-20-4622), with $p<0.05$ considered significant. Results: Significant differences were observed between active and inactive groups for various parameters ($p<0.001$). HBeAg-positive participants showed elevated hepatic parameters compared to HBeAg-negative ($p<0.001$). ALT levels correlated with differences in biochemical profiles ($p<0.001$). Cirrhosis prevalence was higher in the active group ($p=0.001$). During 12-month follow-up, treated subjects exhibited elevated hepatic parameters ($p<0.001$). HBeAg-positive cases had increased complications ($p=0.001$). ALT level alterations impacted clinical profiles significantly ($p<0.001$). Results suggest diverse outcomes in HBV patients, emphasizing the need for individualized management. Conclusion: This study underscores the heightened risk of hepatic complications in active CHB patients, emphasizing the poorer prognosis in HBeAg-negative cases. While strides have been made in comprehending the disease's behavior, the complex natural history of HBV necessitates ongoing exploration and learning.

Citation: Lefebvre S, Dubois L, Leroy C. Towards Optimal Care: Hepatitis B in Saudi Arabia - Initiatives for Clinical Excellence and Malpractice Prevention: Insights from the Systematic Observatory Liver Disease (SOLID) Registry. Canad. Jr. Clin. Perf. Eval., 2024, 1, 3, 35-52

Academic Editor: Paul Weber
Received: 16 January 2024
Revised: 27 February 2024
Accepted: 2 March 2024
Published: 24 March 2024

1. Introduction

Hepatitis B virus (HBV) infection remains a pressing global public health concern, contributing significantly to chronic liver diseases and associated morbidity and mortality.[1] The World Health Organization (WHO) estimates that approximately 257 million people are living with chronic hepatitis B (CHB), resulting in an annual toll of 887,000 HBV-related deaths, mainly attributed to cirrhosis and hepatocellular carcinoma.[2,3] Regions such as Southeast Asia, China, Pacific Islands, and Sub-Saharan Africa maintain high HBV prevalence, with Saudi Arabia and Jordan classified as highly endemic in the Middle East, while Turkey and Pakistan exhibit intermediate endemicity.[4]

CHB poses a multifaceted clinical challenge due to its global distribution and diverse clinical manifestations. Geographical variations in the incidence and prevalence of CHB underscore its complexity.[5] In Saudi Arabia, the prevalence has shown a notable decline from historical rates of 8.3% to a recent 1.3%, attributed to a successful national vaccination program and improved healthcare measures. Despite this progress, CHB remains a dynamic and often asymptomatic condition, demanding a nuanced understanding of its natural course and potential long-term impacts.[6]

The diagnosis of CHB relies on a combination of clinical, biochemical, serological, and histological parameters. HBV infection encompasses a spectrum of clinical outcomes, from inactive carriers with normal histology to advanced cirrhosis.[7] This silent epidemic can progress silently, leading to severe conditions such as liver cancer or cirrhosis, especially in individuals with persistently elevated liver enzymes or high viremia. The highly contagious nature of HBV, transmitted through direct contact with infected bodily fluids, further complicates its management.[8]

CHB-induced liver injuries are primarily mediated by the host's immune responses against HBV, triggering cytotoxic T lymphocyte-mediated responses and hepatocyte apoptosis.[9] The natural history of CHB unfolds across various phases, with distinct clinical and virologic characteristics. Notably, the transition from the early replicative phase to late non-replicative phases is accompanied by HBeAg seroconversion and potential disease remission.[10] Cirrhosis development rates differ between HBeAg-positive and -negative patients, emphasizing the importance of understanding these distinct phases in managing long-term outcomes.[11]

Despite the progress in global guidelines, the natural history of CHB in Saudi Arabia lacks comprehensive, long-term studies to elucidate disease behavior.[12] This study addresses this knowledge gap by analyzing a substantial cohort of CHB patients over an extended follow-up duration. Investigation parameters include serological markers, liver biopsy, and non-invasive assessments like serum-based scores (APRI, FIB-4) and transient elastography (fibro scan).[13]

Treatment decisions are typically guided by evidence of disease activity, emphasizing the importance of monitoring serum ALT, HBV DNA, and liver fibrosis. Inactive disease phases, characterized by immune tolerance, necessitate observational approaches, aligning with international guidelines. However, gaps persist in understanding the potential reactivation of inactive disease and the disease course in patients on long-term antiviral therapy.[14]

This study evaluates non-invasive serum scores' performance, including APRI and FIB-4, in assessing liver fibrosis. Transient elastography by fibro scan is scrutinized for its diagnostic efficacy, with studies showing promising results in detecting significant fibrosis and cirrhosis. The comprehensive assessment of these parameters contributes to a more nuanced understanding of CHB progression and enhances clinical decision-making in the Saudi population. Our study aims to bridge existing knowledge gaps in the natural history of CHB in Saudi Arabia by conducting a detailed analysis of a large patient cohort. The findings are poised to contribute valuable insights into disease behavior, treatment outcomes, and factors influencing CHB progression, ultimately informing more effective clinical management strategies.

2. Methods

Study Participants Study population

We collected Data from the SOLID (Saudi observatory liver disease) registry for all CHB patients in the database from January 2008 to December 2019. This registry is a multicenter, nationwide liver disease research database (SOLID Registry, 2017). This

database collects data and track follow up of patients registered regularly. During this period, we collected data from all CHB patients.

This study design has been divided into two parts:

Part 1:

Demographics and Clinical Characteristics

Demographic and clinical characteristics of the study cohort were meticulously retrieved from the comprehensive SOLID (Saudi Observatory Liver Disease) registry, spanning the period from January 2008 to December 2019. This extensive database, recognized for its multicenter and nationwide coverage of liver disease, facilitated the extraction of pertinent information related to patient demographics. Variables such as age, gender, and baseline laboratory values, including ALT, AST, alkaline phosphatase, albumin, bilirubin, platelets, and baseline HBV PCR, were systematically collected. Additionally, the presence of comorbidities was thoroughly documented, shedding light on the health status of participants. The identified comorbidities, encompassing [list specific comorbidities], were considered in the subsequent analyses to better understand their potential impact on study outcomes.

Inclusion criteria:

Patient included were adults with confirmed CHB, which is defined as HBsAg positive for more than six months, serum HBV DNA varies from undetectable to several billion IU/Ml (lower values of 2,000 to 20,000 IU per mL often occur with HBeAg-negative chronic hepatitis B), normal or elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels, and liver biopsy results showing chronic hepatitis with variable necroinflammation and/or fibrosis. Here all patients of CHB were included who visited any of the centers included in the SOLID registry during the study time period. This is the first part of this study; it was cross-sectional in nature from a significant SOLID cohort.

Exclusion criteria:

Patients were excluded from the study if they were co-infected with hepatitis C, hepatitis D, or human immunodeficiency virus (HIV), the presence of other severe systemic disease or other major organ dysfunction, exposure to potential hepatotoxic medication within the previous 6 months, or having received medications that can affect the platelet levels. AS well patient was excluded if there is signifying deficiency on the baseline parameters, such as viral load, liver enzymes.

Classification of patients: According to the baseline HBeAg, HBV DNA, AST, ALT, platelets data, and non-invasive markers and/or liver biopsy, the study subjects were classified into different groups: inactive disease or active disease (either HBeAg-positive or HBeAg-negative hepatitis B). Patients with active disease were patients with serum HBV DNA >20,000 IU/mL in HBeAg-positive CHB and >2000 IU/mL in HBeAg-negative with intermittently or persistently elevated ALT and/or AST levels, and inactive disease if they were inactive carriers (if they had HBeAg negative, anti-HBe positive, serum HBV DNA <2000 IU/mL, persistently normal ALT and/or AST levels and liver biopsy or non-invasive testing show variable levels of fibrosis). Subjects were classified as having cirrhosis when there is confirmed cirrhosis on histology or non-invasive markers. We compared groups based on two different methods for evaluating ALT levels: the standard laboratory reference range, which defines normal as ALT<61 IU/L, and the range proposed by a recent national study which sets upper limits of normal ALT at 33 IU/l for men and 22 IU/l for women.

Patients were divided into active and inactive disease based on the criteria of international guidelines. Used criteria for chronic hepatitis B (CHB) activity are outlined in guidelines such as those provided by organizations like the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), or the World Health Organization (WHO).

Typically, criteria for active CHB may include elevated levels of serum HBV DNA, abnormal liver function tests (such as alanine aminotransferase or ALT), and the presence of specific markers like hepatitis B e antigen (HBeAg). Inactive disease is often characterized by lower viral loads, normal or minimally elevated liver enzymes, and the absence of certain disease markers. We included as well in this group some patients who have been labeled as active based on clinical judgment and started treatment by the treating physician

Part 2:

In this study, we included those subjects who had follow-up (FU) in the center > 12 months. We considered untreated patients with immunotolerance and those patients who were inactive carriers. Treated patients were with the active disease based on the guideline's definition and treated during follow-up: patients whose initial assessment showed the non-indication of treatment, however during FU, their status changed to active based on clinical judgment, and thereafter, needed treatment.

In Part 2 of the study, subjects with a follow-up duration exceeding 12 months were included, specifically focusing on untreated patients exhibiting immunotolerance and those identified as inactive carriers. For treated patients, adherence to guideline-defined active disease criteria and subsequent treatment during follow-up were considered. Noteworthy is the stability of the study design, with no alterations made during the update, ensuring consistency in the evaluation of disease progression, treatment responses, and associated outcomes. This standardized 12-month follow-up period in Part 2 facilitates a comprehensive understanding of the long-term dynamics in untreated and treated cohorts, shedding light on the natural course of chronic hepatitis B and the efficacy of interventions over time.

During the follow-up period, specific treatment protocols were implemented based on established guidelines for chronic hepatitis B (CHB). Treatment initiation criteria were aligned with international guidelines, considering factors such as serum HBV DNA levels exceeding 20,000 IU/mL in HBeAg-positive CHB and greater than 2,000 IU/mL in HBeAg-negative CHB, along with intermittently or persistently elevated ALT and/or AST levels. Clinical judgment played a crucial role, as some patients labeled as active based on this judgment received treatment initiated by the treating physician.

Notably, the adherence to treatment protocols remained consistent throughout the follow-up period, with no modifications introduced during clinical judgment. This approach ensured the reliability and comparability of treatment outcomes, providing a robust basis for evaluating the impact of the prescribed interventions on disease progression and other relevant endpoints. The standardized treatment criteria and the absence of modifications contribute to the study's internal validity and the reliability of conclusions drawn regarding the efficacy of treatment strategies in managing CHB over the extended follow-up duration.

Outcomes of Interest

Here we considered outcome variables as baseline measures, including data regarding patient demographics; baseline laboratory tests regarding liver functions, viral serology; Liver fibrosis and disease status categories; active and inactive disease status. We assessed differences in non-invasive biomarkers of fibrosis (e.g., AST to Platelet Ratio

Index (APRI), Fibrosis-4 (FIB-4), and NAFLD fibrosis (NFS) scores). As already indicated above, we considered follow-up measures, additionally Data regarding treatment; Loss of virus spontaneously or in response to treatment, and development of complications such as HCC, death, or loss of follow up.

Sensitivity analyses

Sensitivity analyses were conducted to rigorously examine the robustness of the study results with respect to comorbidities. Variations in the definitions and classifications of comorbidities were explored, allowing for a comprehensive assessment of their influence on the observed outcomes. Subgroup analyses were performed, stratifying the data based on the presence or absence of specific comorbidities, providing insights into potential differential effects within distinct subgroups. Different statistical models were employed to evaluate the stability of associations with comorbidities, ensuring that results were not overly dependent on a particular modeling approach. Robustness was further assessed by employing diverse methods for handling missing data, including multiple imputations and sensitivity analyses with varying assumptions. Outlier analyses were conducted to identify and examine any disproportionate impact of outliers on the observed associations. Temporal changes were considered by dividing the dataset into different time periods, elucidating whether results remained consistent over time and exploring potential influences of evolving comorbidity prevalence. Alternative outcome measures related to comorbidities were also employed to validate the results and assess the consistency of findings across different metrics. Additionally, external validation using independent datasets or published studies was undertaken to further corroborate the stability of associations and enhance the generalizability of the study's conclusions. These sensitivity analyses collectively fortified the robustness of the study results, providing a thorough understanding of the impact of comorbidities on the investigated outcomes.

Laboratory Values

The following laboratory values were included: ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, bilirubin, platelets, baseline HBV PCR, HBV DNA levels. Aspartate transaminase-to-platelet ratio index (APRI) was calculated with the following formula: ((AST/ULN AST) x100)/Platelets (109/L)). APRI score greater than 1.0 has a sensitivity of 76% and specificity of 72% for predicting cirrhosis. APRI score greater than 0.7 has a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis. APRI > 1.5 is the cut-off value for significant fibrosis, whereas a score <0.5 can rule it out.[15]

Quantification of HBV DNA levels in the plasma was performed by real-time polymerase chain reaction (RT-PCR) on COBAS AmpliPrep COBAS TaqMan HBV test and Abbott m 2000 sp/m 2000 rt with a lower detection limit of 10 IU/mL.[16]

Non-Invasive Biomarkers of Fibrosis

Age and other laboratory values extracted from the database were used to calculate APRI, FIB-4, and NFS scores at the time of diagnosis. Formulas that were used to calculate these respective non-invasive biomarkers of fibrosis can be found elsewhere.[17] The fibrosis index (FIB-4) is based on the four factors and calculated by the following formula: Age (yr.) x AST (IU/ml)/PLT (x109/L) x ALT (IU/ml) 1/2. A FIB-4 score <1.45 has a negative predictive value of 90% in patients with advanced fibrosis. FIB-4 score >3.25 has a 97% specificity and a positive predictive value of 65 % of patients.[18]

The actual formulas for calculating APRI, FIB-4, and NFS scores were as follows:

- Aspartate Aminotransferase-to-Platelet Ratio Index (APRI):

  \text{APRI} = \frac{\text{AST} (\text{aspartate aminotransferase})}{\text{Upper Limit of Normal AST}} \times \frac{100}{\text{Platelet count (10^9/L)}}

  Note: AST should be expressed as a ratio to the upper limit of normal (ULN).[19]

- Fibrosis-4 (FIB-4) Index:

  \text{FIB-4} = \frac{\text{Age (years)} \times \text{AST}}{\text{Platelet count (10^9/L)} \times \sqrt{\text{ALT}}}

  NAFLD [20]

- Fibrosis Score (NFS):

  \text{NFS} = -1.675 + 0.037 \times \text{Age (years)} + 0.094 \times \text{BMI} + 1.13 \times \text{Impaired fasting glucose/diabetes (yes=1, no=0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{Platelet count (10^9/L)} - 0.66 \times \text{Albumin}[21]

  Note: BMI stands for Body Mass Index.

Abdominal ultrasound, as well as transient elastography, was performed on all patients. The liver stiffness was measured with transient elastography (TE), fibro scan (EchoSensR, Paris, France), and expressed in kilopascals (kPa). The mean value was obtained from 10 performed measures, with a success rate of more than 60% and interquartile range (IQR) < 0.25.

Ethical approval: This study was approved by Institutional Review Board (IRB Approval Number: E-20-4622), and informed consent was obtained from all patients prior to study enrollment. The data accessed from the SOLID Registry complied with relevant data protection and privacy regulations.

Statistical analysis

Data were analyzed using SPSS version 21.5 (IBM, Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) for continuous variables and frequencies (percentages, %) for categorical variables. The independent samples T-test and chi-square were used to compare means and frequencies between patient groups, respectively. The Mann-Whitney U test was used for non-normally distributed continuous variables. Figures were plotted in MS Excel. Significance was set at $p<0.05$.

3. Results

Part 1:

A total of 1564 patients with HBV were reported in the active (n=346) and inactive (n=1218) in Table 1. Before dividing into active and inactive groups, we describe individuals' background, characteristics, and HBV profile at baseline in Table 1. The average age was 41 years, the male patients were 62.5%, whereas the female participant was 37.5%. The average BMI of this cohort was 28.4 kg/m^2. The HBeAg positive participant was 12.1%, and the rest 87.9% was negative. Mean (SD) values of crucial biochemical parameters were: ALT (IU/L): 52.1 (64.4); AST (IU/L): 32.5 (47.8); ALP (IU/L): 89.9 (27.3): Bil (mg/dl): 10.9 (14.7); PLT (109/ L): 243.5 (72.4); Albumin: 38.8 (5.1). Baseline HBV PCR was Positive (<2000) in half of the participants. The mean baseline HBV DNA value (IU/Ml) was 4.9 x107 (5.9 x 108). 6.4% of patients presented with cirrhosis. 82.8% patients had FIB4 at <1.30. As shown in Table 1, 81.6% of subjects had Baseline APRI<0.5. The mean value (SD) of the Baseline AST/ALT ratio was 0.7 (0.4).

Baseline HBeAg with Positive was five times higher in active group (32.4%) compared to inactive group (6.3%). The important hepatic function parameters were significantly higher in active group than in inactive group at baseline (Mean (SD), P value) (active vs. inactive: ALT: 88.5 (119.1) vs. 41.7 (28.6), p=0.001; AST: 59.7 (90.5) vs. 24.8 (18.4), p=0.001; ALP: 96.5 (31.8) vs. 88.1 (25.6), p=0.001; Bilirubin: 15.8 (29.6) vs. 9.5 (4.1), p=0.001). Some biochemical parameters were decreased in active group compared to inactive group (active vs. inactive: PLT: 207.5 (77.7) vs. 253.9 (67.3), p=0.001; Albumin: 36.8 (6.9) vs. 39.4 (4.3), p=0.001). (Table 1)

Baseline HBV PCR with Positive (>20000) was 58.9% in the active group, whereas 13.2% in the inactive group, and this distribution pattern was statistically significant. Baseline HBV DNA values (IU/Ml) were about 3-fold higher in the inactive group than the active group with statistical significance (p =0.001) (Table 1).

The common complication baseline Cirrhosis was active group 92 (26.6%) & inactive group 8 (0.7%), (p=0.001) (Table 1). Baseline FIB4 <1.30 was the most prevalent in both active and inactive groups, although statistically significant. Similarly, baseline APRI <0.5 was the most prevalent in both active and inactive groups, although statistically significant. The baseline AST/ALT ratio did not alter significantly between active and inactive groups. Thus, in summary, all the investigated parameters were significantly different in between the active and inactive groups besides the baseline AST/ALT ratio (Table 1).

Table 1: Comparison of baseline parameters of patients with active versus inactive disease

Factors	**Total (*n*=1564)**	**Active (*n*=346)**	**Inactive (*n*=1218)**	**P-value**
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	
Age	41.0 (13.7)	43.4 (14.6)	40.3 (13.3)	0.002
Gender				0.001
Male, *n* (%)	978 (62.5)	250 (72.3)	728 (59.8)	
Female, *n* (%)	586 (37.5)	96 (27.8)	490 (40.2)	
BMI	28.4 (6.1)	27.8 (5.9)	28.6 (6.2)	0.050
HB e Ag				0.001
Negative, n (%)	1375 (87.9)	234 (67.6)	1141 (93.7)	
Positive, n (%)	189 (12.1)	112 (32.4)	77 (6.3)	
ALT (IU/L)	52.1 (64.4)	88.5 (119.1)	41.7 (28.6)	0.001
AST (IU/L)	32.5 (47.8)	59.7 (90.5)	24.8 (18.4)	0.001
ALP (IU/L)	89.9 (27.3)	96.5 (31.8)	88.1 (25.6)	0.001
Bil (mg/dl)	10.9 (14.7)	15.8 (29.6)	9.5 (4.1)	0.001
PLT (109/ L)	243.5 (72.4)	207.5 (77.7)	253.9 (67.3)	0.001
Albumen	38.8 (5.1)	36.8 (6.9)	39.4 (4.3)	0.001
Baseline HBV PCR				0.001
Negative, n (%)	161 (10.3)	0 (0.0)	161 (13.2)	
Positive (<2000), n (%)	787 (50.3)	83 (23.9)	704 (57.8)	
Positive (2000-20000), n (%)	251 (16.1)	59 (17.1)	192 (15.8)	
Positive (>20000), n (%)	365 (23.3)	204 (58.9)	161 (13.2)	
Baseline HBV DNA values (IU/Ml)	4.9 x107 (5.9 x 108)	1.1 $x10^8$ (9.5 x 108)	3.1 $x10^7$ (4.5 x 108)	0.001
Baseline Cirrhosis				0.001
Non-Cirrhosis, *n* (%)	1445 (92.4)	235 (67.9)	1.210 (99.3)	
Cirrhosis, *n* (%)	100 (6.4)	92 (26.6)	8 (0.7)	
Decompensated Cirrhosis, *n* (%)	19 (1.2)	19 (5.5)	0 (0.0)	
Baseline FIB4	0.9 (1.1)	1.5 (1.9)	0.7 (0.6)	0.001
<1.30, *n* (%)	1295 (82.8)	212 (61.3)	1083 (88.9)	0.001
1.30 –3.25, *n* (%)	157 (10.0)	80 (23.1)	77 (6.3)	
>3.25, *n* (%)	112 (7.2)	54 (15.6)	58 (4.8)	
Baseline APRI	0.3 (0.4)	0.6 (0.7)	0.3 (0.2)	0.001
<0.5, *n* (%)	1276 (81.6)	189 (54.6)	1087 (89.2)	0.001
0.5 to 1.5, *n* (%)	161 (10.3)	92 (26.6)	69 (5.7)	
>1.5, *n* (%)	127 (8.1)	65 (18.8)	62 (5.1)	

Next, in Table 2, we compared the study subjects dividing into positive and negative groups based on HBeAg. The HBeAg negative were 1375 cases (87.9%) and positive 189 (12.1%) (Table 2). The mean age was significantly different between the groups (positive vs. negative; mean age: 35.8 vs. 41.6) (p=0.001). Among negative subjects, male: female was 836 (60.8%): 539 (39.2%) and among positive subjects, male: female was 142(75.1%):47(24.8%) (p=0.001). There was no statistical difference in BMI between the negative and positive groups (negative vs. positive; 28.4 (6.0) vs. 28.2 (6.6), p=0.784.

Table 2. Description of individuals' background, characteristics, and HBV profile at baseline, stratified by HB e Ag (n=1564)

Factors	Negative (*n*=1375)	Positive (*n*=189)	P-value
	Mean (SD)	*Mean (SD)*	
Age	41.6 (13.7)	35.8 (12.3)	0.001
Gender			0.001
Male, *n* (%)	836 (60.8)	142 (75.1)	
Female, *n* (%)	539 (39.2)	47 (24.8)	
BMI	28.4 (6.0)	28.2 (6.6)	0.784
ALT (IU/L)	45.9 (44.2)	97.3 (133.8)	0.001
AST (IU/L)	29.3 (39.8)	55.4 (82.3)	0.001
ALP (IU/L)	88.6 (26.4)	99.2 (31.1)	0.001
Bil (mg/dl)	10.4 (11.6)	14.0 (27.9)	0.002
PLT (109/ L)	245.3 (72.3)	229.8 (71.3)	0.006
Albumen	39.0 (4.9)	37.5 (6.0)	0.001
Baseline HBV PCR			0.001
Negative, n (%)	160 (11.6)	1 (0.5)	
Positive (<2000), n (%)	773 (56.2)	14 (7.4)	
Positive (2000-20000), n (%)	242 (17.6)	9 (4.7)	
Positive (>20000), n (%) DELETE	200 (14.5)	165 (87.3)	
Baseline HBV DNA values (IU/Ml)	9.9 x10^6 (1.4 x 10^8)	3.1 x10^7 (4.5 x 10^8)	0.001
Baseline Cirrhosis			0.001
Non-Cirrhosis, *n* (%)	1,285 (93.4)	160 (84.6)	
Cirrhosis, *n* (%)	75 (5.4)	25 (13.2)	
Decompensated Cirrhosis, *n* (%)	15 (1.0)	4 (2.1)	
Baseline FIB4	0.8 (1.0)	1.0 (1.4)	0.023
<1.30, *n* (%)	1150 (83.6)	145 (76.7)	0.028
1.30 –3.25, *n* (%)	128 (9.3)	29 (15.3)	
>3.25, *n* (%)	97 (7.1)	15 (7.9)	
Baseline APRI	0.3 (0.4)	0.5 (0.5)	0.001
<0.5, *n* (%)	1163 (84.6)	113 (59.8)	0.001
0.5 to 1.5, *n* (%)	106 (7.7)	55 (29.1)	
>1.5, *n* (%)	106 (7.7)	21 (11.1)	

ALT and AST were almost double in the positive group than in the negative. Baseline ALT in negative group 45.9 (44.2) and ALT in positive group 97.3 (133.8), p=0.001 and baseline AST in negative group 29.3 (39.8) and AST in positive group 55.4 (82.3), p=0.001; Alkaline phosphatase in the negative group (ALP) 88.6 (26.4) and ALP in positive group 99.2 (31.1), p=0.001 (Table 2); Baseline bilirubin was higher in the positive group compared to that of the negative group (negative vs. positive; 10.4 (11.6) vs. 14.0 (27.9), p=0.002). Platelets and albumin were a bit decreased in the positive group compared negative group. Baseline HBV PCR with Positive (>20000) was 87.3%, whereas Positive (<2000) was 7.4% in HBeAg positive group, and this pattern of distribution was statistically significant. Baseline HBV DNA mean value (IU/Ml) was significantly higher in positive group than in negative group (positive vs. Negative: 3.1 x107 (4.5 x 108) vs 9.9 x106(1.4 x 108), p=0.001). The prevalence of baseline cirrhosis was more than 2.5-fold higher in the positive group compared to the negative group (negative vs. positive; 5.4% vs. 13.2%), which was statistically highly significant (p=0.001). Baseline FIB4 <1.30 was the most prevalent in both negative and positive groups, although statistically significant. Baseline APRI was significantly higher in positive group than in negative group (mean value: negative vs. positive: 0.3 (0.4) vs. 0.5 (0.5) (p=0.001). Although the Baseline AST/ALT ratio was near similar in negative and positive groups, they were statistically significant.

Figure 1 (A) showed the percentage of HBeAg among the FIB-4 category. % of the HBeAg, either positive or negative, was the highest in FIB-4 <1.30 and then gradually decreased with the increased value of FIB4. If we express in another way, % of HBeAg was greater in FIB-4 1.30-3.25 and FIB >3.25 category compared to the percentage of negative group. Figure 1 (B) showed the percentage of HBeAgeither positive or negative, subjects among APRI categories. There were fewer HBeAgpositive subjects APRI <0.5 category compared to that of the negative group. %HBeAg positive subjects were almost four times higher than the percentage of negative subjects in the APRI 0.5-1.5 category. In APRI >1.5 categories, % of HBeAg-positive subjects was higher than the negative subjects.

Table 3 was based on the group stratified by ALT level. Age (years) and BMI (kg/m2) were statistically significant between normal and up normal group (age; normal vs. up normal; 41.4 (13.5) vs. 38.7 (14.1), p=0.002 and BMI; normal vs. up normal; 28.6 (6.2); vs 27.4 (5.5), p=0.003) (Table 3). The percentage of HBeAg positive subjects was more in the normal group (32.9%) than in the normal group (7.3%). Baseline AST, ALP and Bilirubin were higher in up normal group compared to those in normal group and statistically significant (AST; normal vs. up normal: 22.9 (12.2) vs. 75 (98.0), p=0.001; ALP: normal vs. up normal: 87.2 (25.0); vs. 101.5 (32.8), p=0.001 and Bil: normal vs. up normal: 9.9 (7.2) vs. 15.3 (30.3), p=0.001). Platelets and albumin were lower in the up normal group compared to the normal group. Baseline HBV PCR with Positive (>20000) was 52.2%, whereas Positive (<2000) was 29.5% in the up normal group, and this pattern of distribution was statistically significant. Baseline HBV DNA mean value (IU/Ml) was significantly higher in normal group than in negative group (up normal vs. normal: 1.3 x108 (1.0 x 109) vs. 3.1 x107(4.4 x 108), p=0.014). The prevalence of baseline cirrhosis was three times higher in the up normal group (14.4%) than in the normal group (4.5%). Baseline FIB4, baseline APRI, baseline AST/ALT ratio were also significantly different between normal and normal groups. The results in Table 3 strongly indicated that ALT level alteration could change clinical to hepatic profiles in CHB.

Table 3. Description of individuals' background, characteristics, and HBV profile at baseline, stratified by ALT (n=1564)

Factors	Normal (*n*=1273)	Abnormal (*n*=291)	P-value	Total (*n*=1564)
	Mean (SD); median (min-max)	*Mean (SD); median (min-max)*		*Mean (SD); median (min-max)*
Age	41.4 (13.5); 40 (18-89)	38.7 (14.1); 35 (18-84)	0.002	41.0 (13.7); 39 (18-89)
Gender			0.001	
Male, *n* (%)	739 (58.0)	239 (82.1)		978 (62.5)
Female, *n* (%)	534 (41.9)	52 (17.8)		586 (37.5)
BMI	28.6 (6.2); 28.1 (14.3-54.8)	27.4 (5.5); 26.6 (14.2-50.4)	0.003	28.4 (6.1)
HBeAg			0.001	
Negative, n (%)	234 (92.6)	195 (67.0)		1375 (87.9)
Positive, n (%)	93 (7.3)	96 (32.9)		189 (12.1)
AST (IU/L)	22.9 (12.2); 20 (9-167)	75.0 (98.0); 44 (10-945)	0.001	32.5 (47.8); 22 (9-945)
ALP (IU/L)	87.2 (25.0); 85 (40-188)	101.5 (32.8); 95 (45-199)	0.001	89.9 (27.3); 87 (40-199)
Bil (mg/dl)	9.9 (7.2); 8.9 (3.3-181.3)	15.3 (30.3); 11.0 (3.4-370.9)	0.001	10.9 (14.7); 9.0 (3.3-370.9)
PLT (109/ L)	248.5 (72.3); 242 (42-733)	221.6 (68.6); 219 (42-429)	0.001	243.5 (72.4); 238 (42-733)
Albumen	39.0 (4.7); 39.6 (12.0-51.8)	37.8 (6.2); 39 (13-50)	0.001	38.8 (5.1); 39.6 (12.0-51.8)
Baseline HBV PCR			0.001	
Negative, n (%)	149 (11.7)	12 (4.1)		161 (10.3)
Positive (<2000), n (%)	701 (55.0)	86 (29.5)		787 (50.3)
Positive (2000-20000), n (%)	210 (16.5)	41 (14.0)		251 (16.1)
Positive (>20000), n (%)	213 (16.7)	152 (52.2)		365 (23.3)
Baseline HBV DNA values (IU/Ml)	3.1 $x10^7$ (4.4 x 10^8); 504.5 (0-1.1 x 10^{10})	1.3 $x10^8$ (1.0 x 10^9); 38000 (0-1.7 x 10^{10})	0.014	4.9 $x10^7$ (5.9 x 10^8); 790 (0-1.7 x 10^{10})
Baseline Cirrhosis			0.001	
Cirrhosis, *n* (%)	58 (4.5)	42 (14.4)		100 (6.4)
Non-Cirrhosis, *n* (%)	1207 (94.8)	238 (81.7)		1445 (92.4)
Decompensated Cirrhosis, *n* (%)	8 (0.6)	11 (3.7)		19 (1.2)
Baseline FIB4	0.8 (0.9); 0.6 (0.1-13.6)	1.3 (1.7); 0.7 (0.1-12.7)	0.001	0.9 (1.1); 0.6 (0.1-13.6)
Baseline APRI	0.2 (0.2); 0.2 (0.1-3.8)	0.7 (0.7); 0.5 (0.1-4.8)	0.001	0.3 (0.4); 0.2 (0.1-4.8)
Baseline AST/ALT ratio	0.7 (0.4); 0.6 (0.2-4.8)	0.5 (0.3); 0.4 (0.1-2,8)	0.001	0.7 (0.4); 0.6 (0.1-4,8)

Part2:

The patients followed up for 12 months have been analyzed in Part2. Here we had total of subjects 699; No Treatment (n=609) and Treatment during FU (n=90) (Table 4). Before dividing into groups based on the receiving treatment or not, here we presented first the follow-up total cohort results. The average age was 41 years, the male participant was 58.8%, whereas the female participant was 41.2%. The average BMI of this cohort was 28.9 kg/m^2. The HBeAg positive participant was 6.2%, and the rest 93.7% was negative. Mean values of crucial biochemical parameters are ALT (IU/L): 44.3 (28.9); AST (IU/L): 23.8 (22.7); ALP (IU/L): 88.7 (24.3): Bilirubin (mg/dl): 9.7 (3.9); Platelets (109/ L): 254.1 (64.2); Albumin: 39.1 (3.7). Baseline HBV PCR was Positive (<2000) in 62.5% of the participants. The mean baseline HBV DNA value (IU/Ml) was 4.9 x10^7 (5.9 x 108). 0.2% of patients presented with cirrhosis. 94.1% of patients had FIB4 at <1.30. As shown in Table 4, 93.6% of subjects had Baseline APRI<0.5. The mean value of the Baseline AST/ALT ratio was 0.6 (0.5).

The important hepatic function parameters were significantly higher in treatment during FU group than in no treatment groups. Mean (SD); ALT in no treatment group 41.8 (25.6) and ALT in treatment during FU group 60.7 (42.1), p=0.001 and AST in no treatment group 22.5 (11.0); and AST in treatment during FU group 33.3 (31.3); p=<0.001; Alkaline phosphates (ALP) in no treatment group 88.5 (24.2); and ALP in treatment during FU group 90.3 (25.0), p=0.525; Bilirubin in no treatment group 9.6 (3.9); & treatment during FU group 10.5 (4.1), p=0.073; platelets in no treatment group 253.6 (63.6); & treatment during FU group 257.7 (68.0), p=0.571;albumin in no treatment group 39.1 (3.6); & albumin in treatment during FU group 38.4 (4.4); p=0.108 (Table 4).

Baseline HBV PCR with Positive (>20000) was 6.5% in the no-treatment group, and 44.4% in treatment during the FU group. This pattern of distribution was statistically significant. Baseline HBV DNA values (IU/Ml) were higher in treatment during the FU group than in the no treatment group with statistical significance (p=0.001). The common complication Baseline Cirrhosis in no treatment group 0 (0.0%) & treatment during FU group was 2 (2.2%), 0.001 (Table 4).

There was no statistical significance between no treatment group and treatment during the FU group of FIB4 <1.30 (no treatment group vs. treatment during FU group: 94.6% vs. 91.1%, p=0.234). APRI (<0.5) was the most prevalent in both groups, although statistically significant. Baseline AST/ALT ratio did not alter significantly between no treatment group and treatment during FU group (Table 4). In more than 80% of cases, both in two groups, a fibro scan was not conducted. In more than 70% of cases of both groups, BSFibroscan data was not available. There was a significant difference in various grades of FSSTIFFNES in the two groups presented in Table 4.

In Table 5, we compared the study subjects regarded as a non-treated group both at baseline and at the end of follow-up. A total patient presented here baseline 609 and FU 609 (Table 5). At the FU time, the number of subjects of HBeAg became higher, and this was significantly higher than that of baseline. The important hepatic function parameters were significantly higher at baseline than at the end of follow-up. Mean (SD); ALT in baseline group 41.8 (25.6) and ALT in FU group 32.3 (17.6), p=0.001; AST in baseline group 22.4 (11.0) and AST in FU group 21.1 (9.1), p=0.007; Alkaline phosphates in baseline group 88.2 (24.0) and ALP in FU group 84.0 (25.2), p=0.001; Albumin in baseline group 38.8 (3.6) & albumin in FU group 37.7 (3.8); p=0.001; Bilirubin in baseline group 41.8 (25.6) & FU group 10.0 (5.1), p=0.128 (Table 5). There was no statistical difference in platelets between baseline and after the FU. Mean (SD); PLT in baseline

group 253.6 (63.7) and PLT in FU group 252.0 (64.9), p=0.437. Baseline HBV PCR with Positive (>20000) was 6.5% in the baseline group and 5.3% in the FU group. This pattern of distribution was statistically significant. In this non-treatment group, no cirrhosis was observed at baseline and FU. Here there was no difference in HVB DNA level for the untreated patients at two-time points. FIB4 was statistically significant at two-time points (baseline vs. FU). APRI was similar in both baseline and FU groups, although statistically significant. Baseline AST/ALT ratio did not alter significantly between baseline and FU group. BSFibroscan (available) was almost double in the FU group than in the baseline group. Baseline BSFibroscan (available) in baseline group 28.5% and FU group 55.8%, p=0. 001. FSSTIFFNES (F0) was the most prevalent in both time points. There was no change in the hepatic complication rate at these two-time points. No hepatic complication was observed between the groups.

Figure 1-4: After we do segregation based on different levels of FIB-4 nad APRI, can we Check predictors of cirrhosis based on APR>1.5 AND OR FIB-4>3.25

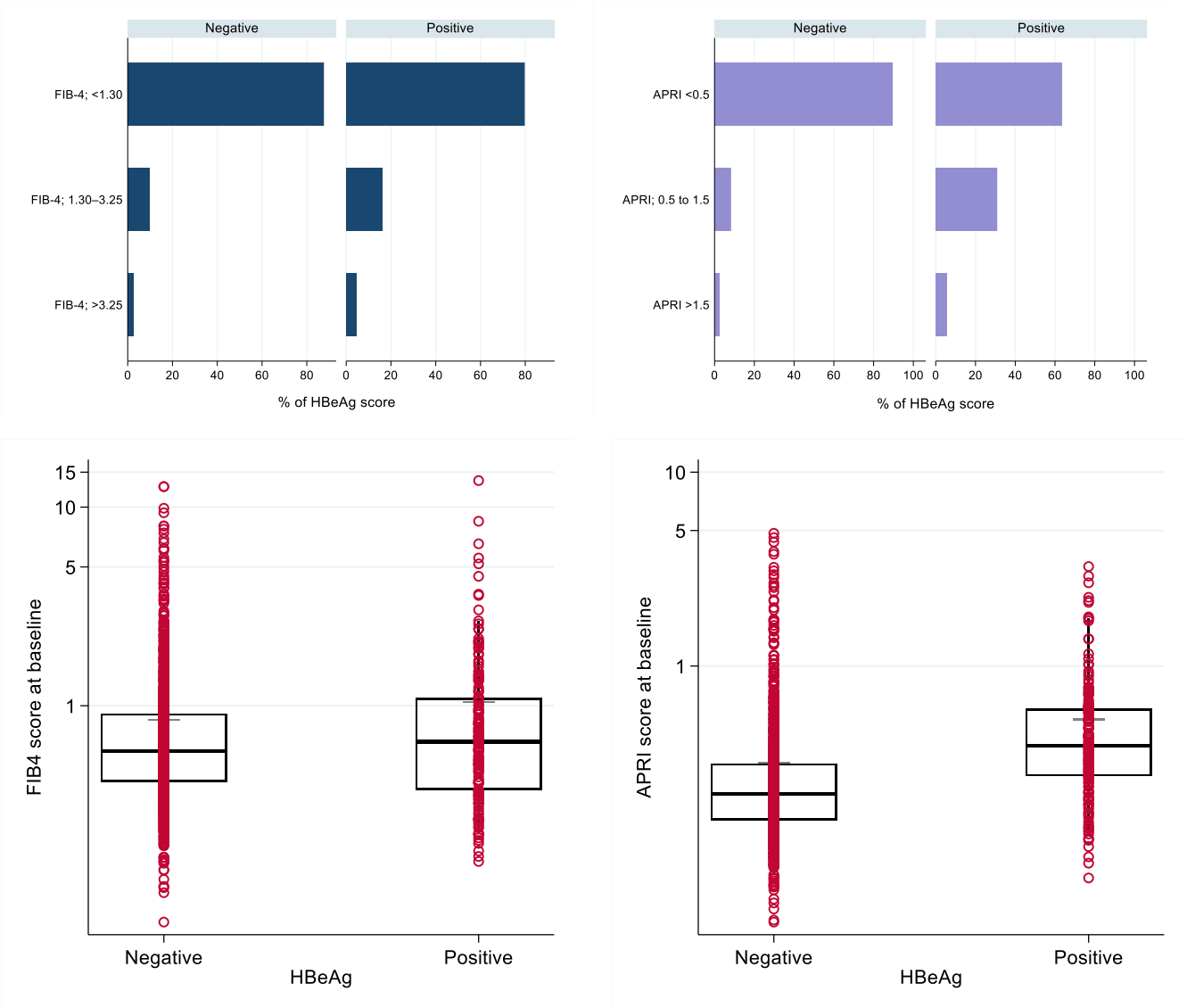

Table 4.

Factors	**No Treatment (*n*=609)**	**Treatment during FU (*n*=90)**	**P-value**	**Total (*n*=699)**
	Mean (SD)	*Mean (SD)*		*Mean (SD)*
Age	41.1 (13.1)	39.1 (13.3)	0.1694	41.0 (13.2)
Gender			0.021	
Male, *n* (%)	348 (57.1)	63 (70.0)		411 (58.8)
Female, *n* (%)	261 (42.8)	27 (30.0)		288 (41.2)
BMI	28.8 (5.7)	29.5 (6.6)	0.3041	28.9 (5.8)
HBeAg			0.001	
Negative, n (%)	588 (96.5)	67 (74.4)		655 (93.7)
Positive, n (%)	21 (3.4)	23 (25.5)		44 (6.2)
ALT (IU/L)	41.8 (25.6)	60.7 (42.1)	0.001	44.3 (28.9)
AST (IU/L)	22.5 (11.0)	33.3 (31.3)	0.000	23.8 (22.7)
ALP (IU/L)	88.5 (24.2)	90.3 (25.0)	0.5255	88.7 (24.3)
Bil (mg/dl)	9.6 (3.9)	10.5 (4.1)	0.0727	9.7 (3.9)
PLT (109/ L)	253.6 (63.6)	257.7 (68.0)	0.5712	254.1 (64.2)
Albumen	39.1 (3.6)	38.4 (4.4)	0.1079	39.1 (3.7)
Baseline HBV PCR				
Negative, n (%)	64 (10.5)	5 (5.5)	0.001	69 (9.8)
Positive (<2000), n (%)	411 (67.4)	26 (28.8)		437 (62.5)
Positive (2000-20000), n (%)	94 (15.4)	19 (21.1)		113 (16.1)
Positive (>20000), n (%)	40 (6.5)	40 (44.4)		80 (11.4)
Baseline HBV DNA values (IU/Ml)	1.98 x10^7 (4.1 x 10^8)	3.1 x107 (4.5 x 10^8)	0.001	4.9 x107 (5.9 x 10^8)
Baseline Cirrhosis			0.001	
Cirrhosis, *n* (%)	0 (0.0)	2 (2.2)		2 (0.2)
Non-Cirrhosis, *n* (%)	609 (100.0)	88 (97.7)		697 (99.7)
Decompensated Cirrhosis, *n* (%)	-	-		
Baseline FIB4	0.6 (0.3)	0.7 (0.6)	0.077	0.6 (0.3)
<1.30, *n* (%)	576 (94.6)	82 (91.1)	0.234	658 (94.1)
1.30 –3.25, *n* (%)	29 (4.8)	6 (6.7)		35 (5.0)
>3.25, *n* (%)	4 (0.7)	2 (2.2)		6 (0.9)
Baseline APRI	0.2 (0.1)	0.3 (0.2)	0.001	0.2 (0.1)
<0.5, *n* (%)	578 (94.9)	76 (84.4)	0.001	654 (93.6)
0.5 to 1.5, *n* (%)	22 (3.6)	10 (11.1)		32 (4.6)
>1.5, *n* (%)	9 (1.5)	4 (4.4)		13 (1.9)
Baseline AST/ALT ratio	0.6 (0.2)	0.5 (0.4)	0.507	0.6 (0.5)
Fibroscan			0.039	
No fibroscan	153 (87.9)	23 (85.1)		176 (87.5)
Significant fibroscan	21 (12.1)	3 (11.1)		21 (11.9)
Advance fibroscan	0 (0.0)	1 (3.7)		1 (0.5)
Total	174 (100.0)	27 (100.0)		201 (100.0)
BSFibroscan				
Available	174 (28.5)	27 (30.0)	0.780	201 (28.7)
Not available	435 (71.4)	63 (70.0)		498 (71.2)
Total	609 (100.0)	90 (100.0)		699 (100.0)
FSSTIFFNES				
F0	106 (60.9)	10 (37.0)	0.007	116 (57.7)
F1	47 (27.0)	13 (48.1)		60 (29.8)
F2	21 (12.1)	3 (11.1)		24 (11.9)
F4	0 (0.0)	1 (3.7)		1 (0.5)
Total	174 (100.0)	27 (100.0)		201 (100.0)
Months after enrolment	-	45.8 (36.1)		-

Table 5. (This is follow up)

Factors	**No Rx (Baseline) (*n*=609)**	**No Rx (FU) (*n*=609) (571)**	**P-value**
	Mean (SD)	*Mean (SD)*	
HBeAg			0.001
Negative, n (%)	588 (96.5)	594 (28.6)	
Positive, n (%)	21 (3.4)	15 (71.4)	
ALT (IU/L)	41.8 (25.6)	32.3 (17.6)	0.001
AST (IU/L)	22.4 (11.0)	21.1 (9.1)	0.007
ALP (IU/L)	88.2 (24.0)	84.0 (25.2)	0.001
Bil (mg/dl)	41.8 (25.6)	10.0 (5.1)	0.128
PLT (109/ L)	253.6 (63.7)	252.0 (64.9)	0.437
Albumen	38.8 (3.6)	37.7 (3.8)	0.001
HBV PCR			0.001
Negative, n (%)	64 (10.5)	123 (20.2)	
Positive (<2000), n (%)	411 (67.4)	384 (63.1)	
Positive (2000-20000), n (%)	94 (15.4)	70 (11.5)	
Positive (>20000), n (%)	40 (6.5)	32 (5.3)	
HBV DNA values (IU/Ml)	1.9 x10^7 (4.1 x10^8)	7181309 (8.7 x10^7)	0.401
Cirrhosis			-
Cirrhosis, *n* (%)			
Non-Cirrhosis, *n* (%)	609 (100)	609 (100)	
Decompensated Cirrhosis, *n* (%)			
FIB4	0.6 (0.3)	0.7 (0.4)	0.001
APRI	0.2 (0.1)	0.2 (0.1)	0.021
AST/ALT ratio	0.6 (0.2)	0.7 (0.2)	0.001
BSFibroscan			0.001
Available	174 (28.5)	340 (55.8)	
Not available	435 (71.4)	269 (44.2)	
FSSTIFFNES			0.001
F0	72 (58.5)	92 (74.8)	
F1	34 (27.5)	25 (20.3)	
F2	17 (13.8)	4 (3.3)	
F3	-	-	
F4	-	-	
Change of status			
Naïve_non-cirrhosis_Unchanged	609 (100)	609 (100)	
HCC	4 (100)	4 (100)	
Yes at FU			

4. Discussion

This is the first study in Saudi Arabia enrolling the most significant number of CHB patients. To the best of our knowledge, this study was the first to describe the natural history of CHB based on various characterization profiles. Our results showed significant differences in the different parameters used in the present study between various chronic hepatitis B infection groups.

This was the first population-based study with long-term follow-up of inactive HBV carriers. In addition, here at the baseline level, we could characterize the features of CHB based on the disease state-active or inactive, HBeAg, and the level of ALT. If we look at all these stratified groups, there were significant differences between groups based on the disease status, HBeAg status, and ALT levels. We considered the clinical profiles, hepatic functional profiles, viral load status, morphological status of the liver.

The relationship between clinical performance evaluation, malpractice prevention, and the study "Unveiling the Tapestry of Hepatitis B in Saudi Arabia: Insights from the Robust Systematic Observatory Liver Disease (SOLID) Registry" lies in several key areas; The SOLID registry provides a comprehensive dataset of chronic hepatitis B (CHB) patients in Saudi Arabia from 2008 to 2019. Through retrospective analysis, the study assesses baseline characteristics and outcomes of CHB patients. Clinical performance evaluation involves analyzing the effectiveness of healthcare interventions, treatment protocols, and patient management strategies. By examining the data from the SOLID registry, researchers can evaluate how well healthcare providers are managing CHB

patients and identify areas for improvement in clinical performance. Understanding the natural course of chronic hepatitis B and the impact of follow-up on disease progression is crucial for preventing malpractice. By analyzing the SOLID registry data, healthcare providers can identify factors associated with poor outcomes in CHB patients, such as delays in diagnosis, inadequate treatment, or lack of follow-up care. This information can help healthcare organizations implement strategies to improve patient care, reduce medical errors, and prevent malpractice lawsuits.

The study provides valuable insights into the prevalence, characteristics, and outcomes of chronic hepatitis B in Saudi Arabia. By understanding the epidemiology and clinical course of HBV infection in the country, healthcare providers can tailor their approaches to diagnosis, treatment, and follow-up care. This can lead to better clinical outcomes, improved patient safety, and reduced risk of malpractice related to hepatitis B management.

The rationale of HBV treatment is to significantly suppress HBV replication and prevent the progression of HBV-mediated liver injury that may cause cirrhosis, liver failure, or HCC.[22] Therefore, the primary goal of HBV treatment should focus on maintaining sustained HBV DNA suppression. This will lead to the other benefits, i.e., the secondary aims of therapy, including the normalization of transaminases, histological improvement, reduction of cirrhosis and the related complications, and the need for liver transplantation.[23] Historically, levels of HBV DNA and ALT and histological activity of liver biopsy has been used as the three main factors to determine if a patient needs HBV treatment or not. HBV DNA level, HBeAg status, degree of hepatic histological activity and fibrosis, and serum transaminases are the most important parameters in determining indication, regimen, and duration of HBV treatment. In the current study also, we investigated all parameters as described in a recent study.[24]

In the current study, in both active and inactive groups, the number of male subjects is greater than the female subjects. The important hepatic functional parameters are significantly lower in the inactive group than in the active group, as also found in a past study.[25] There is evident variation in HBeAg cases between active and inactive groups. The detection of HBV infection is vital for diagnosis, follow up the study and for controlling spread in community with the limited spectrum of disease range for chronic, often progress to liver cirrhosis, and HCC depends on the interplay between viral and host factors.[26] Dividing into the active and inactive group, the present study revealed HBeAg positivity in 12.1% of patients previously diagnosed serologically, diagnosed on clinical pictures as HBV infection.[27] Of these patients, baseline cirrhosis in active group 92 (26.6%) & inactive group 8 (0.7%) (Table 1). Although it is well-known that inactive carriers develop hepatic complications, complication like cirrhosis is rare in the inactive group in the present study. Low levels of HBV DNA in PCR-based assays are also found in current study inactive subjects.[28] It is said that carriers of inactive HBV have a substantial risk of hepatocellular carcinoma and liver-related death compared with individuals not infected with HBV. But here in the current study comparison, the hepatic complications are significantly smaller than the active group. Baseline FIB4 is another investigating parameter in the current study, which is about 2-fold increase in the active group than in the non-active group.[29] In addition, no baseline HBV PCR was negative in the active group. Carriers of inactive HBV have a substantial risk of hepatocellular carcinoma and liver-related death compared with individuals not infected with HBV. Inactive carriers of HBV have an increased HCC incidence and liver-related mortality than HBsAg-seronegative controls. In our current result, the Baseline AST/ALT ratio did not differ between the groups.[30]

In general, patients with HBeAg-positive CHB present with positive HBsAg and HBeAg in serum that is associated with active HBV replication, infectivity, and hepatic

inflammation. Depending on the mode of HBV transmission, spontaneous seroconversion from HBeAg to anti-HBe is variable.[31] Most patients who underwent seroconversion remain sustained remission of HBV infection that is associated with normal transaminases and a low or undetectable level of serum HBV DNA, although serum HBsAg may remain positive. In the present study, we also found a significantly higher level of hepatic enzymes in HBeAg positive cases than negative cases, as also seen in past studies. Baseline HBV DNA values (IU/Ml) were significantly different in positive cases than in negative cases as consistent with past study.[32] Here the complication cirrhosis is also higher in the positive group than in the negative group. In fact, HBeAg negative chronic hepatitis B (CHB) is a frequent, progressive, and difficult-to-cure phase of CHB. The impact of genders revealed 62.5% males and 37.5% females (Table 2); this was inconsistent with what was reported in the past study and agreed with Disease and European Association for the study of the Liver guidelines in HBeAg-positive patients with cirrhosis, even after HBeAg seroconversion, and HBeAg-negative patients unless HBsAg loss and/or seroconversion occurs.[33]

Serum ALT level has been a significant predictor for CHB. Here the most striking feature has been observed in the findings of HBV DNA level. The upregulated ALT group had a tremendous elevation of HBV DNA level, which has been consistent with past studies.[34] In addition, the % of HBeAg result was also consistent with the past finding. The hepatic complication has been seen related to the ALT levels in the current study. Theoretically, serum levels of ALT, an enzyme that is released from hepatocytes during liver injury, should reflect the degree of liver damage. There are very few studies investigating together ALT, HBeAg, and liver histology.[35] In the current study, we found a higher level of FIB4 in the ALT elevated group with statistical significance. There has also been a remarkable difference in Baseline HBV PCR in the normal and elevated levels of ALT groups. Our study has extensively described all the crucial parameters related to hepatic function and morphology-based on the ALT level. For liver biopsy, ALT level has been considered a great parameter.[36]

In this large retrospective cohort study, we present follow-up data. The present study also investigated the effects of 12 months following up in between the inactive group and the inactive groups turned to the active group and received the treatment. In a study, we found a significant number of patients with CHB (23 %) who were not initially treatment eligible later met treatment criteria in longer-term follow-up. While the majority of patients remained treatment ineligible by guideline recommendations, a sizeable proportion (23 %, 95 % CI 18-27 %) of patients subsequently met treatment eligibility in study follow-up.[37] Here in the current study, HBeAg status remains the predominant character in both inactive and treated groups during follow-up. HBeAg-positive cases number were more significant in the treatment group during follow-up than in the inactive group. In fact, HBeAg and HBV DNA have been considered important factors during follow-up. ALT again significantly higher in the follow-up group receiving treatment than the inactive group. Together, HBV DNA level remains at the elevated site in the FU group with treatment, which is expected and consistent with past studies.[38]

In addition, here, we also made a comparison of the non-treated group between baseline and at FU. Hepatic enzymes were significantly decreased at FU end in comparison to baseline. Here 2.2% non-treated group developed hepatic complication at the end of follow up. Baseline HBV PCR Positive (>20000) became 44.4% at the end of FU.[39]

Limitations, in the present study, we don't have the data on HBsAg data. Several non-invasive models have been developed to stage liver fibrosis, including FibroTest, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, AST to platelet index, fibrosis index based on 4 factors (FIB-4). Here in serum Serum biochemistry,

although we included aspartate transferase (AST) and ALT, -glutamyl transpeptidase, alkaline phosphatase, albumin, globulins, total bilirubin; but we did not check prothrombin time, and -1 fetoprotein. HBsAg, antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen (antiHBc), anti-HBe, antibody to HCV, antibody to hepatitis D virus, and antibody to human immunodeficiency virus were not detected in the present study. We also did not stratify baseline HBV DNA in this study. Here we did not show any analysis of HBV DNA level and the incidence of hepatic complications. The present study also did not current result in the gender stratification, and indeed past study had shown the risk for hepatocellular carcinoma was statistically significantly higher among women with chronic or active HBV infections and among those with persistent HBV infection or who underwent HBsAg sero-clearance during follow-up than among HBV-unexposed women. Genetic features including HBV genotype and basal core promoter A1762T/G1764A mutant and precore G1896A mutant were documented as predictors of HCC risk. The present study also did not include the behavioural risk factors data like smoking, alcohol drinking. In addition, there was no information on genotypes in the current study. In addition, here, the follow-up time was shorter in comparison to already published articles. The study also lacked the regional variation on CHB inside Saudi Arabia. Although continuous follow-up of HBV DNA and ALT is important, the present study took the data only after the end of 12 months of treatment. The present study also did not mention the treatment type in the FU group.

The relative risk for individuals with chronic HBV infection of developing progressive liver disease and HCC varies greatly, based largely on disease activity and level of viral replication, and may be predicted by their phenotype. Similar types of observation have also been shown in the present study. The hepatocellular complications depend on various factors. It is possible too that the use of a fixed low value to define normal ALT value may have artificially inflated the size of the indeterminant group, but this issue still persists even when using the laboratory-specific definition of normal ALT. However, a major shortcoming was the development of antiviral resistance, after which HBV DNA levels generally rose and the biochemical and histologic features worsened.

5. Conclusion

Our study represents the largest cohort analysis of chronic hepatitis B (CHB) in Saudi Arabia, providing a detailed understanding of disease characteristics and complications. Through rigorous stratified analyses, we quantified substantial variations in key parameters among study groups, underscoring the heterogeneous nature of CHB. These findings hold clinical relevance, offering insights for personalized patient management based on disease activity, HBeAg levels, and ALT levels. While our study contributes significantly, acknowledging limitations is crucial. Future research should address these constraints and explore additional avenues to enhance our understanding of CHB in the Saudi Arabian context. By doing so, we aim to facilitate more targeted interventions and improved patient outcomes in the management of this complex and diverse disease. In summary, the study contributes to clinical performance evaluation and malpractice prevention by providing insights into the management of chronic hepatitis B in Saudi Arabia. By leveraging the data from the SOLID registry, healthcare providers can optimize their practices, enhance patient care, and minimize the risk of malpractice associated with hepatitis B management.

References

1 Aljumah AA, Babatin M, Hashim A, Abaalkhail F, Bassil N, Safwat M, Sanai FM. Hepatitis B care pathway in Saudi Arabia: Current situation, gaps and actions. Saudi J Gastroenterol. 2019 Mar-Apr;25(2):73-80. doi: 10.4103/sjg.SJG_421_18. PMID: 30720000; PMCID: PMC6457186.

2 Hyun Kim B, Ray Kim W. Epidemiology of Hepatitis B Virus Infection in the United States. Clin Liver Dis (Hoboken). 2018 Aug 22;12(1):1-4. doi: 10.1002/cld.732. PMID: 30988901; PMCID: PMC6385902.
3 Amponsah-Dacosta E. Hepatitis B virus infection and hepatocellular carcinoma in sub-Saharan Africa: Implications for elimination of viral hepatitis by 2030? World J Gastroenterol. 2021 Sep 28;27(36):6025-6038. doi: 10.3748/wjg.v27.i36.6025. PMID: 34629817; PMCID: PMC8476331.
4 Sagnelli C, Pisaturo M, Curatolo C, Codella AV, Coppola N, Sagnelli E. Hepatitis B virus/hepatitis D virus epidemiology: Changes over time and possible future influence of the SARS-CoV-2 pandemic. World J Gastroenterol. 2021 Nov 14;27(42):7271-7284. doi: 10.3748/wjg.v27.i42.7271. PMID: 34876788; PMCID: PMC8611207.
5 Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. World J Gastroenterol. 2014 May 14;20(18):5427-34. doi: 10.3748/wjg.v20.i18.5427. PMID: 24833873; PMCID: PMC4017058.
6 Alasiri AA, Mohammed V. Healthcare Transformation in Saudi Arabia: An Overview Since the Launch of Vision 2030. Health Serv Insights. 2022 Sep 3;15:11786329221121214. doi: 10.1177/11786329221121214. PMID: 36081830; PMCID: PMC9445529.
7 Abaalkhail F, Elsiesy H, AlOmair A, Alghamdi MY, Alalwan A, AlMasri N, Al-Hamoudi W; Saudi Association for the Study of Liver Diseases and Transplantation (SASLT). SASLT practice guidelines for the management of hepatitis B virus. Saudi J Gastroenterol. 2014 Jan-Feb;20(1):5-25. doi: 10.4103/1319-3767.126311. PMID: 24496154; PMCID: PMC3952421.
8 Committee on a National Strategy for the Elimination of Hepatitis B and C; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine; Buckley GJ, Strom BL, editors. Eliminating the Public Health Problem of Hepatitis B and C in the United States: Phase One Report. Washington (DC): National Academies Press (US); 2016 Jun 1. 2, The Elimination of Hepatitis B. Available from: https://www.ncbi.nlm.nih.gov/books/NBK368066/
9 Khanam A, Chua JV, Kottilil S. Immunopathology of Chronic Hepatitis B Infection: Role of Innate and Adaptive Immune Response in Disease Progression. Int J Mol Sci. 2021 May 23;22(11):5497. doi: 10.3390/ijms22115497. PMID: 34071064; PMCID: PMC8197097.
10 Croagh CM, Lubel JS. Natural history of chronic hepatitis B: phases in a complex relationship. World J Gastroenterol. 2014 Aug 14;20(30):10395-404. doi: 10.3748/wjg.v20.i30.10395. PMID: 25132755; PMCID: PMC4130846.
11 Liaw YF. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. Hepatol Int. 2009 Sep;3(3):425-33. doi: 10.1007/s12072-009-9140-3. Epub 2009 Jun 24. PMID: 19669245; PMCID: PMC2748370.
12 Abdo AA, Hassanain M, AlJumah A, Al Olayan A, Sanai FM, Alsuhaibani HA, Abdulkareem H, Abdallah K, AlMuaikeel M, Al Saghier M, Babatin M, Kabbani M, Bazarbashi S, Metrakos P, Bruix J; Saudi Association for the Study of Liver Diseases and Transplantation; Saudi Oncology Society. Saudi guidelines for the diagnosis and management of hepatocellular carcinoma: technical review and practice guidelines. Ann Saudi Med. 2012 Mar-Apr;32(2):174-99. doi: 10.5144/0256-4947.2012.174. PMID: 22366832; PMCID: PMC6086640.
13 Zeng X, Xu C, He D, Li M, Zhang H, Wu Q, Xiang D, Wang Y. Performance of several simple, noninvasive models for assessing significant liver fibrosis in patients with chronic hepatitis B. Croat Med J. 2015 Jun;56(3):272-9. doi: 10.3325/cmj.2015.56.272. PMID: 26088852; PMCID: PMC4500965.
14 Suk-Fong Lok A. Hepatitis B Treatment: What We Know Now and What Remains to Be Researched. Hepatol Commun. 2018 Nov 15;3(1):8-19. doi: 10.1002/hep4.1281. PMID: 30619990; PMCID: PMC6312657.
15 Esmaeelzadeh A, Saadatnia H, Memar B, Mokhtari Amirmajdi E, Ganji A, Goshayeshi L, Meshkat Z, Pasdar A, Vosoughinia H, Farzanehfar M, Tehranian S, Ghaffarzadehgan K, Rajabzadeh F, Ahadi M. Evaluation of serum HBV viral load, transaminases and histological features in chronic HBeAg-negative hepatitis B patients. Gastroenterol Hepatol Bed Bench. 2017 Winter;10(1):39-43. PMID: 28331563; PMCID: PMC5346823.
16 Chevaliez S, Bouvier-Alias M, Laperche S, Pawlotsky JM. Performance of the Cobas AmpliPrep/Cobas TaqMan real-time PCR assay for hepatitis B virus DNA quantification. J Clin Microbiol. 2008 May;46(5):1716-23. doi: 10.1128/JCM.01248-07. Epub 2008 Feb 20. PMID: 18287319; PMCID: PMC2395079.
17 Alswat K, Sanai FM, Al-Hamoudi W, Ismail M, Dahlan Y, AlGhamdi HS, Altraif I, Alalwan A, Babatin MMA, Alqahtani SA. Clinical and Metabolic Characteristics of Non-Alcoholic Fatty Liver Disease Patients in Saudi

Arabia: Data from the Systematic Observatory Liver Disease (SOLID) Registry. Diabetes Metab Syndr Obes. 2021 Mar 16;14:1167-1175. doi: 10.2147/DMSO.S300051. PMID: 33762835; PMCID: PMC7982437.

18 Dimzova M, Kondova-Topuzovska I, Bosilkovski M, Ivanovski L, Milenkovic Z, Semenakova-Cvetkovska V, Orovcanec N. Noninvasive Biomarkers in Assessment of Liver Fibrosis in Patients with HBeAg Negative Chronic Hepatitis B. Open Access Maced J Med Sci. 2018 Jun 8;6(6):1052-1058. doi: 10.3889/oamjms.2018.122. PMID: 29983800; PMCID: PMC6026435.

19 Jain P, Tripathi BK, Gupta B, Bhandari B, Jalan D. Evaluation of Aspartate Aminotransferase-to-Platelet Ratio Index as a Non-Invasive Marker for Liver Cirrhosis. J Clin Diagn Res. 2015 Nov;9(11):OC22-4. doi: 10.7860/JCDR/2015/13944.6814. Epub 2015 Nov 1. PMID: 26672800; PMCID: PMC4668451.

20 Kuo YH, Kee KM, Hsu NT, Wang JH, Hsiao CC, Chen Y, Lu SN. Using AST-platelet ratio index and fibrosis 4 index for detecting chronic hepatitis C in a large-scale community screening. PLoS One. 2019 Oct 22;14(10):e0222196. doi: 10.1371/journal.pone.0222196. PMID: 31639131; PMCID: PMC6805051.

21 Zhu X, Yan H, Chang X, Xia M, Zhang L, Wang L, Sun X, Yang X, Gao X, Bian H. Association between non-alcoholic fatty liver disease-associated hepatic fibrosis and bone mineral density in postmenopausal women with type 2 diabetes or impaired glucose regulation. BMJ Open Diabetes Res Care. 2020 Aug;8(1):e000999. doi: 10.1136/bmjdrc-2019-000999. PMID: 32759166; PMCID: PMC7409963.

22 Alonso S, Guerra AR, Carreira L, Ferrer JÁ, Gutiérrez ML, Fernandez-Rodriguez CM. Upcoming pharmacological developments in chronic hepatitis B: can we glimpse a cure on the horizon? BMC Gastroenterol. 2017 Dec 21;17(1):168. doi: 10.1186/s12876-017-0726-2. PMID: 29268704; PMCID: PMC5740721.

23 Liaw YF. Impact of therapy on the outcome of chronic hepatitis B. Liver Int. 2013 Feb;33 Suppl 1:111-5. doi: 10.1111/liv.12057. PMID: 23286854.

24 Liu C, Wang L, Xie H, Zhang L, Wang B, Luo C, Wang S, Tang M, Fu Z, Ruan H, Liu Z, Wei L, Yi W, Xie Y. The relationship between serum hepatitis B virus DNA level and liver histology in patients with chronic HBV infection. PLoS One. 2018 Nov 7;13(11):e0206060. doi: 10.1371/journal.pone.0206060. PMID: 30403735; PMCID: PMC6221304.

25 Kwon OS, Kim YK, Her KH, Kim HJ, Lee SD. Physical activity can reduce the prevalence of gallstone disease among males: An observational study. Medicine (Baltimore). 2020 Jun 26;99(26):e20763. doi: 10.1097/MD.0000000000020763. PMID: 32590752; PMCID: PMC7329018.

26 Premkumar M, Chawla YK. Should We Treat Immune Tolerant Chronic Hepatitis B? Lessons from Asia. J Clin Exp Hepatol. 2022 Jan-Feb;12(1):144-154. doi: 10.1016/j.jceh.2021.08.023. Epub 2021 Aug 27. PMID: 35068795; PMCID: PMC8766700.

27 Sunbul M, Leblebicioglu H. Distribution of hepatitis B virus genotypes in patients with chronic hepatitis B in Turkey. World J Gastroenterol. 2005 Apr 7;11(13):1976-80. doi: 10.3748/wjg.v11.i13.1976. PMID: 15800989; PMCID: PMC4305720.

28 Sharma SK, Saini N, Chwla Y. Hepatitis B virus: inactive carriers. Virol J. 2005 Sep 28;2:82. doi: 10.1186/1743-422X-2-82. PMID: 16191199; PMCID: PMC1253537.

29 Chen JD, Yang HI, Iloeje UH, You SL, Lu SN, Wang LY, Su J, Sun CA, Liaw YF, Chen CJ; Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HBV (REVEAL-HBV) Study Group. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology. 2010 May;138(5):1747-54. doi: 10.1053/j.gastro.2010.01.042. Epub 2010 Jan 28. PMID: 20114048.

30 Koc ÖM, Robaeys G, Topal H, Bielen R, Busschots D, Fevery J, Koek GH, Nevens F. Outcome in Caucasian patients with hepatitis B e antigen negative chronic infection: A long-term observational cohort study. J Med Virol. 2020 Dec;92(12):3373-3380. doi: 10.1002/jmv.25950. Epub 2020 May 12. PMID: 32343427; PMCID: PMC7687269.

31 Martin P, Lau DT, Nguyen MH, Janssen HL, Dieterich DT, Peters MG, Jacobson IM. A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: 2015 Update. Clin Gastroenterol Hepatol. 2015 Nov;13(12):2071-87.e16. doi: 10.1016/j.cgh.2015.07.007. Epub 2015 Jul 15. PMID: 26188135.

32 Liaw YF. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. Hepatol Int. 2009 Sep;3(3):425-33. doi: 10.1007/s12072-009-9140-3. Epub 2009 Jun 24. PMID: 19669245; PMCID: PMC2748370.

33 Saikia N, Talukdar R, Mazumder S, Khanna S, Tandon R. Management of patients with HBeAg-negative chronic hepatitis B. Postgrad Med J. 2007 Jan;83(975):32-9. doi: 10.1136/pgmj.2006.044826. PMID: 17267676; PMCID: PMC2599959.

34 Chae HB, Hann HW. Time for an active antiviral therapy for hepatitis B: An update on the management of hepatitis B virus infection. Ther Clin Risk Manag. 2007 Aug;3(4):605-12. PMID: 18472982; PMCID: PMC2374938.

35 Vachon A, Osiowy C. Novel Biomarkers of Hepatitis B Virus and Their Use in Chronic Hepatitis B Patient Management. Viruses. 2021 May 21;13(6):951. doi: 10.3390/v13060951. PMID: 34064049; PMCID: PMC8224022.

36 Tan YW, Zhou XB, Ye Y, He C, Ge GH. Diagnostic value of FIB-4, aspartate aminotransferase-to-platelet ratio index and liver stiffness measurement in hepatitis B virus-infected patients with persistently normal alanine aminotransferase. World J Gastroenterol. 2017 Aug 21;23(31):5746-5754. doi: 10.3748/wjg.v23.i31.5746. PMID: 28883700; PMCID: PMC5569289.

37 Ismailova G, Wagenmakers MAEM, Brusse E, van der Ploeg AT, Favejee MM, van der Beek NAME, van den Berg LEM. Long-term benefits of physical activity in adult patients with late onset Pompe disease: a retrospective cohort study with 10 years of follow-up. Orphanet J Rare Dis. 2023 Oct 11;18(1):319. doi: 10.1186/s13023-023-02924-x. PMID: 37821981; PMCID: PMC10566098.

38 Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560-1599. doi: 10.1002/hep.29800. PMID: 29405329; PMCID: PMC5975958.

39 Asgharian A, Askari G, Esmailzade A, Feizi A, Mohammadi V. The Effect of Symbiotic Supplementation on Liver Enzymes, C-reactive Protein and Ultrasound Findings in Patients with Non-alcoholic Fatty Liver Disease: A Clinical Trial. Int J Prev Med. 2016 Mar 10;7:59. doi: 10.4103/2008-7802.178533. PMID: 27076897; PMCID: PMC4809112.